

DETAILED ACTION

This Action is in response to the communication filed on 1/19/2010.

The amendment filed 1/19/2010 is acknowledged and has been entered.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Status of the Claims

Claims 1-9, 11-19, 24, 26-38, 42-45, 53-62 are currently pending.

Claims 1-8, 11, 13-18, 26, 28-35, 38, 42-45 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10/9/2007.

Claims 9, 12, 19, 24, 27, 36, 37, 53-62 are examined herein.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 9, 12, 19, 24, 27, 36, 37, 54-60, 62 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for antisense-mediated inhibition of

p66shc expression *in vitro* or by direct delivery *in vivo* (without therapeutic treatment), does not reasonably provide enablement for antisense-mediated inhibition of p66shc expression *in vivo* by systemic administrations or for methods of treating disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The above invention is drawn to methods of inhibiting the expression of p66shc in cells or tissues comprising contacting said cells or tissues with nucleic acid compositions that hybridize to sequences encoding p66shc (SEQ ID NO:2). The claims of the above invention are also drawn to methods of treating an animal having vascular complications of diabetes, wherein said compositions are administered to animals such that expression of p66shc is inhibited. The language of said claims encompasses both *in vivo* and *in vitro* activity. The specification discloses a working example where the p66shc gene is knocked-out in MEF cells (*in vitro*), as well as in transgenic mice (*in vivo*) wherein p66shc is not expressed due to disruption of the p66shc gene.

The specification does not provide any working examples demonstrating that antisense nucleic acid sequences can be effectively used in an animal to block p66shc expression **sufficient to result in the required outcome** (e.g., treatment of disease, increase in resistance to oxidative stress, decrease in ROS). Furthermore, the specification as filed does not provide any guidance or examples that would enable a skilled artisan to successfully use the disclosed compounds or methods of using said compounds in *in vivo* environments for the desired result. Additionally, a person skilled in the art would recognize that predicting the efficacy of an antisense compound *in vivo* based solely on its gene disruption models is highly problematic.

Thus, although the specification prophetically considers and discloses general methodologies of using the claimed constructs *in vivo* or in methods of inhibition or treatment, such a disclosure would not be considered enabling since the state of antisense-mediated gene inhibition is highly unpredictable. It is acknowledged that one of skill in the art would recognize that antisense oligonucleotides could be used to inhibit expression of a target gene *in vitro*, in non-therapeutic methods, with a reasonable expectation of success.

The factors listed below have been considered in the analysis of enablement:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The following references are cited herein to illustrate the state of the art of antisense treatment.

A recent (2002) article by Braasch et al. emphasizes that major obstacles persist in the art: "gene inhibition by antisense oligomers has not proven to be a robust or generally reliable technology. Many researchers are skeptical about the approach and it has been suggested that many published studies are at least partially unreliable" (Pg. 4503, para. 1 and 2). Braasch et al. goes on to identify factors that contribute to the unpredictable efficacy of antisense compounds *in vivo*: poor antisense oligonucleotide access to sites within the mRNA to be targeted, difficulties with delivery to and uptake by cells of the antisense oligos, toxicity and immunological problems caused by antisense oligos, and artifacts created by unpredictable binding of antisense compounds to systemic and cellular proteins.

Regarding the difficulties of predicting whether antisense oligonucleotides can access sites within their target mRNA, Braasch et al. explains, “it has been difficult to identify oligonucleotides that act as potent inhibitors of gene expression, primarily due to difficulties in predicting the secondary structures of RNA (Pg. 4503, para. 1 and 2). Branch adds that “internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules” (Page 45, third column). Additionally, in a review of the potential use of antisense oligos as therapeutic agents, Gewirtz et al. teach that the inhibitory activity of an oligo depends unpredictably on the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target. (Page 3161, second and third columns).

The uptake of oligonucleotides by cells has been addressed by Agrawal, who states, “[o]ligonucleotides must be taken up by cells in order to be effective....several reports have shown that efficient uptake of oligonucleotides occurs in a variety of cell lines, including primary cells whereas other reports indicate negligible cellular uptake of oligonucleotides. Cellular uptake of oligonucleotides is complex process; it depends on many factors, including the cell type, the stage of the cell cycle, the concentration of serum. It is therefore, difficult to generalize that all oligonucleotides are taken up in all cells with the same efficiency” (Page 378). “[M]icroinjection or using lipid carriers to supply an oligonucleotide in cell culture increases the potency of the oligonucleotide in cell culture, but it is not clear how relevant this approach is for *in vivo* situations.” (Page 379).

Braasch et al. discuss the non-specific toxicity effects of *in vivo* antisense administration; “even when active oligomers are discovered, the difference in oligonucleotide dose required to

inhibit expression is often not much different than doses that lead to nonselective toxicity and cell death...oligonucleotides can bind to proteins and produce artifactual phenotypes that obscure effects due to the intended antisense mechanism” (Pg. 4503, para. 1 and 2). Branch affirms that “non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, These effects must be explored on a case by case basis” (Page 50), while Tamm et al. states that “[i]mmune stimulation is widely recognized as an undesirable side-effect...the immunostimulatory activity of a phosphorothioate-modified oligonucleotide is largely unpredictable and has to be ascertained experimentally” (page 493, right column).

Further, Branch reasons that “the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available” (Page 46, second column). Tamm et al. concludes by stating that until “the therapeutic activity of an antisense oligonucleotide is defined by the antisense sequence, and thus is to some extent predictable...antisense will not be better than other drug development strategies, most of which depend on an empirical approach.”

The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* treatment of disease, or *in vivo* methods of inhibition, as exemplified in the references above.

Furthermore, one skilled in the art would not accept on its face the examples given in the specification of the inhibition of p66shc expression *in vivo* using gene disruption techniques as being correlative or representative of the successful *in vivo* use of antisense compounds or

treatment of any and/or all conditions or diseases suspected of being associated with p66shc expression. This is particularly true in view of the lack of guidance in the specification and known unpredictability associated with the efficacy of antisense in treating or preventing any conditions or disease suspected of being associated with a particular target gene *in vivo*. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with appropriate *in vivo* delivery and treatment effects provided by antisense administered, and specifically regarding the instant compositions and methods claimed.

Furthermore, as indicated above, the *in vivo* results indicated in the working examples were obtained in knock-out mice. It is noted that Crystal (1995) teaches, "Humans are not simply large mice", and points out that, "predictions from gene transfer studies in experimental animals have not been borne out in human safety and efficacy trials" (see pg 409, col. 1-2). Therefore, results obtained in mice cannot be extrapolated to humans with a reasonable expectation of success.

The claims are drawn very broadly to methods of treating cells *in vivo* or to treating or preventing a condition or disease suspected of being associated with p66shc expression in humans. Since the specification fails to provide any guidance for the successful treatment or prevention of such a disease, and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention to its full scope, using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice

the invention as claimed *in vivo* would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that are successfully delivered to target sites in appropriate cells and/or tissues. In the absence of any real guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

Response to Arguments

2. Applicant's arguments filed 1/19/2010 have been fully considered. Applicants are persuasive to the extent that the specification provides an enabling disclosure for *in vitro* embodiments as well as *in vivo* embodiments but only where the *in vivo* methods are limited to direct delivery to the target and without therapeutic effect. As such, the scope of the enabled embodiments has been changed as indicated in the rejection set forth above.
3. Regarding the presently held non-enabled embodiments, Applicant argues, in summary, that delivery is not an issue based on the state of the art at the time of invention, the amount of any additional experimentation is not undue, and not all claims (e.g., claim 9, 12, 58) require a therapeutic effect. These arguments have been fully considered but are not persuasive.
4. Regarding the argument that delivery is not an issue it is noted that, given the broadest reasonable interpretation, the claims encompass methods where an antisense nucleic acid molecule is administered by any route of administration, including systemic administration. Applicant does not take issue with this interpretation of the claims. Applicants refer to prior art references in support of their position. Regarding the references submitted 1/19/2010, the references only provide evidence that enables delivery of antisense oligonucleotides by direct

delivery to the target tissue. For instance, the references which demonstrate delivery to the liver (Graham, Lu, and Puglielli references) show that the antisense oligonucleotides were delivered by intravenous (IV) administration, which is commensurate with directly delivery to the liver. Importantly, the cited references do not show that IV administration could be used to successfully deliver an effective amount of antisense oligonucleotide to any other tissue. Furthermore, the cited references do not show that other routes of administration, such as subcutaneous or topical administration (which are encompassed by the claims) would result in delivery to the liver or any other distant tissue. References are also cited which utilize nude mice as animal models (Higgins, Hirao); however, nude animals have an impaired immune system and therefore are not considered enabling for systemic delivery in humans in view of the problems associated with an immune response (as indicated in the rejection). In other words, the references cited in the rejection demonstrate that the immune response is a problem for systemic delivery, and references which utilize a nude mouse for systemic delivery do not demonstrate how to overcome this problem because the nude mice do not have a fully functioning immune response. Regarding the Phillips reference, it is noted that this Phillips only shows direct delivery to the target tissue (brain and heart tissue) which is non-dividing tissue. Phillips does not demonstrate systemic delivery to distant tissues nor does Phillips indicate that the AAV can be used to deliver to dividing tissue, which is encompassed by the claims (e.g., see claim 27 which specifically indicates cancers). With respect to the argument that some claims do not require a therapeutic effect, it is noted that all of the rejected claims encompass *in vivo* embodiments, and it is clear from the disclosure that the *in vivo* embodiments are intended to encompass therapeutic treatment. Considering the art recognized problems of therapeutic

treatment as set forth in the rejection and considering the disclosure of the instant application (which provide no working examples of effective therapeutic treatment, in vivo) and the cited prior art, it is clear that additional experimentation is required to use the claimed invention to the full scope encompassed by claims. Furthermore, considering the problems recognized in the art, the amount of additional experimentation is not considered routine. In order to practice the invention to its full scope, the quantity of experimentation required would require the *de novo* determination of formulations with acceptable toxicity and immunogenicity that can successfully deliver antisense molecules to target cells and/or tissues by means other than direct delivery; and would have to show a therapeutic effect in the treated subject. In the absence of any real guidance from the specification, the amount of experimentation is considered to be undue.

5. Therefore, Applicant's arguments as they apply to the instant rejection are not persuasive.

Claim Objections

6. Claims 53, 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. E. ANGELL whose telephone number is 571-272-0756. The examiner can normally be reached on Monday-Thursday 7:00 a.m.-5:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's acting supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J. E. ANGELL/
Primary Examiner, Art Unit 1635